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Role of Monocarboxylate Anion Transporter 8 (MCT8) in Thyroid Hormone Transport: Answers from Mice

The physiological significance of thyroid hormone transporters in the cell membrane has been demonstrated recently with the identification of mutations in the human monocarboxylate anion transporter 8 (MCT8) (1) (2). Mutations of this transporter are associated with a form of X-linked mental retardation, severe neurological impairment, and an unusual pattern of thyroid hormone concentrations in blood. As described by Dumitrescu *et al.* in this issue of *Endocrinology* (3), deletion of the *Mct8* gene in mice faithfully reproduces the altered thyroid hormone concentrations observed in patients, although no obvious signs of neurological impairment are observed in the mutant mice. The altered thyroid hormone concentrations in blood and tissues seem to be due to the simultaneous elevation in the activity of deiodinases type 1 (D1) and 2 (D2) as a consequence of tissue-specific thyroid hormone availability consequent to different dependency on Mct8 for thyroid hormone uptake.

Until recently, the mechanism of thyroid hormone entry into cells was not clear. It was assumed that the lipophilic nature of thyroid hormones facilitated passive diffusion through the lipid bilayer. In support of this idea was the lack of evidence for saturable transport after administration of graded doses of thyroid hormones *in vivo*. However, specific transport mechanisms could be demonstrated for T_4 and T_3 in a variety of cultured cellular systems. Kinetic properties of high-affinity membrane transporters were described and later on characterized as distinct molecular entities (for a review see Ref. 4). The membrane transporters for thyroid hormones belong to several families including the Na^+-dependent organic anion transporter, the Na+-independent organic anion transporting polypeptides, the heterodimeric amino acid transporters, and the MCTs. These transporters have a wide range of tissue distribution, with overlapping patterns of expression in most of them.

The important role of the transporters in thyroid pathophysiology received strong support with the identification of patients harboring mutations of the MCT8. The *MCT8* gene is located in the X chromosome and encodes a 12-segment transmembrane protein expressed in brain, liver, kidney, thyroid, heart, pituitary, and other tissues. So far it is known to be specific for iodothyronines, with higher affinity for T_3 than for T_4 (5). The patients with mutations of this gene are affected by a form of an X-linked mental retardation syndrome combined with an unusual pattern of circulating thyroid hormones, with high T_3 and low T_4 and rT_3. The neurological impairment is present in early infancy and includes global developmental delay with poor head control, mental retardation, and various degrees of motor abnormalities including spastic quadriplegia.

Inactivating mutations of the *MCT8* gene could explain the thyroid phenotype as a consequence of the restricted passage of T_4 and T_3 to cells. Results *in vitro* showed that cultured skin fibroblasts isolated from the patients had a decreased uptake of both T_4 and T_3 (6). D2 activity was increased up to 8-fold in the cells, an expected consequence of decreased availability of T_4, which regulates D2 degradation through the proteasome pathway (7). The authors proposed that increased conversion of T_4 to T_3 in tissues, together with a decreased T_3 reuptake, was responsible for the decreased circulating T_4 and increased T_3. Deficient uptake of T_3 by neurons could also provide an explanation for the thyroid syndrome as well as being the determinant cause for the neurological impairment in patients. In the brain, most T_3 is formed locally by D2-mediated conversion of T_4 to T_3. This enzyme is predominantly expressed in glial cells, namely astrocytes and third ventricle tanycytes (8). It is likely that the passage of T_4, and T_3, to astrocytes through the blood-brain barrier is not affected in the patients because the brain endothelial cells express another transporter, from the Na^+-independent organic anion transporting polypeptides family. However, MCT8 is expressed in neurons and, therefore, neuronal uptake of T_3 is likely to be impaired in the patients (9). In addition, because neurons express the inactivating type 3 deiodinase (D3), which degrades T_3 to T_2, decreased degradation of T_3 could also account for the elevated blood levels of this hormone.

The Mct8 knockout mice generated by Dumitrescu *et al.* and reported in this issue (3) are an excellent tool to analyze the pathophysiology of the syndrome. The most important observation is that, indeed, deletion of the *Mct8* gene leads to thyroid function abnormalities similar to those observed in the humans. Male mice with the genotype $Mct8^{-/y}$ have elevated T_3 and reduced T_4 and rT_3 in blood. Importantly, $Mct8^{-/-}$ females present similar abnormalities, discarding any gender-specific differences that could influence the phenotype. The authors compare the effect of different doses of T_3 administered to the wild-type and the mutant mice. Several conclusions could be drawn from these experiments. First, the authors demonstrate a relative pituitary resistance to thyroid hormone, because a higher dose of T_3 was needed to suppress TSH in the mutant mice than in the wild-type mice. This experiment indicates that the effect of T_3 on TSH suppression requires transport through Mct8. Actually the transporter is expressed in the anterior pituitary, though not in hormone producing, but in stellate cells (10). Second, they showed that the elevated T_3 levels are due primarily to increased production from T_4. The reason is that, in the T_3-treated mice, basal concentrations of T_3 and the disappear-

Abbreviations: D1, Deiodinase type 1; D2, deiodinase type 2; D3, deiodinase type 3; MCT-8, monocarboxylate anion transporter 8.

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ance rate of the hormone in serum and liver were similar in mutant and wild-type mice, in a situation where T_4 was undetectable in both strains of mice. Therefore, T_4 is needed to maintain the high T_3 concentration in the mutant mice.

Indeed, a crucial aspect of the thyroid phenotype of the mutant mice is the coexistence of "hyperthyroid" and "hypothyroid" tissues, leading to a simultaneous elevation of D1 and D2 activities, respectively, in those tissues. In the liver, where transporters other than Mct8 are expressed, the elevation of circulating T_3 induces a clear thyrotoxic state, as shown by markers of thyroid hormone action in this organ. D1, a sensitive marker of thyroid status in the liver, was up-regulated. The elevated activity of this enzyme further contributes to the syndrome by increasing conversion of T_4 to T_3 and increasing degradation of rT_3.

D2 activity was highly increased in the brain, as a response to cellular hypothyroidism. The highly increased D2 activity in brain is likely due to the decreased availability of T_4 to the astrocytes secondary to a decreased circulating T_4. The contribution of the brain to the thyroid syndrome is complex. D2 and Mct8 are expressed in different cells (9), and entry of T_4 and T_3 to D2-expressing astrocytes through the blood-brain barrier should, in principle, not be compromised, as it takes place through a different transporter. An elevation of D2 activity in these cells should be a late event in the syndrome, following the decreased T_4 supply. Another type of D2-expressing cells, the tanycytes, also express Mct8. These cells presumably get T_4 from the cerebrospinal fluid, via the choroid plexus, a site of prominent Mct8 expression. Therefore, it is likely that tanycyte D2 is increased in the early phases of the syndrome, but its possible contribution to the syndrome is unknown.

The contribution of D2 expressed in other tissues such as the heart, muscle, or skin is probably also relevant to explain the role played by D2 in the initial phases of the syndrome, through a mechanism of increased T_3 production and decreased T_3 reuptake, as described above.

The role of D3 is not clear. It appears likely that a restriction in T_3 transport to cells expressing D3 could explain the elevation of T_3 concentrations through decreased degradation. Such a restricted transport of T_3 was demonstrated by the lack of D3 induction in *Mct8*$^{-/y}$ mice treated with T_3. However, the data show that, under conditions of undetectable T_4 in the plasma, the concentrations reached by T_3 at different times after administration were not different in normal than in the mutant mice.

Despite that *Mct8* deletion reproduced the thyroid phenotype in mice, no obvious signs of neurological disturbances were observed. The mice seem to behave normally, without obvious motor abnormalities. Of course, a more detailed behavioral evaluation is needed. As pointed out by the authors (3), in mice it is difficult to reproduce other situations resulting from decreased thyroid hormone supply to the human brain. In terms of basal T_3 concentration, the brains of the mutant mice are probably not as strongly hypothyroid, as in other situations such as Pax8 deletion (11). The secondary increase in D2 activity may provide sufficient T_3 to normalize basal expression of T_3-regulated genes and prevent the harmful effects of unliganded T_3 nuclear receptor (12, 13).

In conclusion, the findings by Dumitrescu *et al.* (3) represent an important step forward in understanding the role of the transporters in thyroid hormone distribution and action and the pathogenesis of the X-linked mental retardation syndrome caused by MCT8 mutations in humans.

Juan Bernal
Instituto de Investigaciones Biomédicas
Consejo Superior de Investigaciones Científicas
Universidad Autónoma de Madrid
28029 Madrid, Spain

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Address all correspondence and requests for reprints to: Prof. Juan Bernal, Instituto de Investigaciones Biomédicas, Arturo Duperier 4, 28029 Madrid, Spain. E-mail: jbernal@iib.uam.es.

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